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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,567	09/01/2000	Adriano Aguzzi	6458.US.01	2914

7590 11/14/2003

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/554,567	AGUZZI ET AL.	
	Examin r	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed August 25, 2003 (Paper No. 26) in response to the Office Action of February 25, 2003 is acknowledged and has been entered. Claims 38-40 have been cancelled. Claims 35-37 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 35-40 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of Applicants amendments canceling the term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen"" from the claims.

The rejection of claims 35-40 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is **withdrawn** in view of Applicants amendments canceling the term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen"" from the claims.

The rejection of claims 35-40 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is **withdrawn** in view of Applicants amendments canceling the term "TSE-infected B-cell antigen" or "TSE-infected T-cell antigen"" from the cliams.

Claim Rejections - 35 USC § 103

The rejection of claims 35-40 under 35 U.S.C. 103(a) as being unpatentable over O'Rourke et al (US Pat No. 6,165,784),and/or Korth et al. (Nature 6 November 1997; 390:74-77), in view of Kuroda et al. (Infection and Immunity 1983; 41:154-61) and/or Manuelidis et al. (Science 1978; 200:1069-1071) **is maintained** for reasons of record.

Applicants arguments have been fully considered but the have failed to persuade the Office to remove the instant rejection. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The claims are broadly drawn to methods for the identification of the presence of transmissible spongiform encephalopathy (TSE) in B cells and/or T cells. The method steps are interpreted broadly (comprising) indicating that the methods may have more steps than those enumerated in the claims. Applicants have added the steps of homoginization, which is given the plain dictionary meaning: to blend into uniform mixture, to reduce to small particles of uniform size and distribute evenly in a liquid (Webster's Collegiate Dictionary 10th edition). The term "proteinase kinase digestion" has not been disclosed in the instant specification (see new

matter rejection below) it is believed that Applicant's meant to us the term "proteinase K" which is an art recognized term describing a serine endopeididase from *Tritirachium album limber*. The term "SDSPG immunoaffinity chromatography blots" also has not been described in the instant specification (see new matter rejection below) this term has been interpreted to mean SDS Page followed by electroblotting of the protein onto a membrane (see specification page 112, example 12).

Kuroda et al. teach that fractionated B cells and T cells obtained from the spleens of mice infected with the causative agent of Creutzfeldt-Jakob disease (CJD), a form of transmissible spongiform encephalopathy (TSE), can be injected into susceptible mice and transmit disease (see entire document, especially Tables 2 and 4). Thus Kuroda et al. teach a method to test for the presence of transmissible spongiform encephalopathy comprising obtaining a sample of spleen, collecting B cells and collecting T cells from the sample, and testing the B cells and/or T cells for the presence of the transmissible spongiform encephalopathy agent. The reference does not teach detecting the TSE agent in the B and or T cells using an immunoblot procedure following proteinase K digestion of the B cell and/or T cell.

Manuelidis et al. teach a method to test for the presence of transmissible spongiform encephalopathy comprising obtaining a sample of whole blood (which is a heterogeneous mixture of cell types and other components), collecting B cells and collecting T cells from the sample by isolating the buffy coat, and testing the B cells and T cells contained within the buffy coat for the presence of transmissible spongiform encephalopathy. Manuelidis et al. attribute their ability to demonstrate the infectivity of blood to an increase in the sensitivity of the assay made possible by collecting a specific fraction of whole blood (that inherently containing the B

cells and T cells) (see entire document, especially the last full paragraph on page 1070). The ability to transmit disease to another animal is a well-established means of testing for the presence of an infectious agent. The white blood cells of the buffy coat of whole blood comprise B cells and T cells. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The reference does not teach detecting the TSE agent in the B and or T cells using an immunoblot procedure following proteinase K digestion of the B cell and/or T cell.

O'Rourke et al. teach methods to test for transmissible spongiform encephalopathy in lymphoid tissue using an antibody that serves as a ligand in various immunoassays, including immunohistochemistry, western immunoblots, and dot blots (see entire document, e.g., "Summary of the Invention"). O'Rourke et al. teach that antibody ligands may be either polyclonal sera or monoclonal antibodies (see entire document, e.g., column 5, especially lines 40-50). PrP-Sc was isolated from the brain of sheep with histopathologic lesions of scrapie by differential centrifugation from a high salt Sarkosyl buffer. Briefly, aliquots of midbrain or brainstem were homogenized in and clarified by centrifugation. The supernatant was centrifuged and the resulting pellet was resuspended and digested with DNaseI and RNase. The buffer was re-adjusted to 3.2 ml TBS/10% NaCl/1% sarkosyl with 10 .mu.g/ml proteinase K and digestion proceeded for 1 hour at 37.degree. C. The reaction was stopped by the addition of Pefabloc to 4 mM. PrP-Sc was pelleted by centrifugation, the pellet was boiled in SDS (5%) sample buffer for 10 minutes. Aliquots equivalent to 125 mg starting material were electrophoresed through a 15% polyacrylamide mini-gel and transferred to PVDF membranes. The filters were developed with monoclonal antibody or a control antibody, goat anti-mouse IgG-HRPO, and a chemiluminescent

substrate (see column 10, lines 34-65). O'Rourke et al. does not teach collecting B cells and/or T cells from a test sample and directly testing these cell types for the presence of transmissible spongiform encephalopathy.

Korth et al. teach a method of detecting transmissible spongiform encephalopathy based upon a monoclonal antibody that is specific for the prion form of PrP (the causative agent in TSEs) versus the cellular form of PrP (see entire document, e.g. Abstract). Korth et al. teach that this antibody can be used to identify the prion form of PrP directly, thus providing a basis for a TSE test in living humans or animals, by lowering the detection threshold needed (see especially paragraph preceding "Methods" on page 77). Korth et al. does not teach collecting B cells and/or T cells from a test sample and directly testing these cell types for the presence of transmissible spongiform encephalopathy.

Thus Kuroda et al. teach that both B cells and T cells can transmit TSE, and Manuelidis et al. teach that it is important to focus on these cellular populations to increase the sensitivity of assays for TSE infectivity. Both O'Rourke et al. and Korth et al. teach methods of detecting the disease form of prion protein after proteinase K digestion followed by SDS-Page electrophoresis and blotting onto a membrane. One of ordinary skill in the art would have had a high expectation of success in applying the techniques taught by O'Rourke et al. or Korth et al. to the infected tissue disclosed by Kuroda et al. or Manuelidis et al. It would have been obvious at the time the invention was made to improve the sensitivity of the TSE tests by collecting samples containing B cells and/or T cells and testing for the presence of TSE using an antibody-based system. The ordinary artisan at the time the invention was made would have been motivated to this in order to avoid having to utilize animals in order to test for infectivity in the B and/or T

cell population. The ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with antibodies. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claims 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection, there is insufficient written description in the specification regarding the terms "proteinase kinase" or "SDSPG immunoaffinity chromatography blots".

The term "proteinase kinase" is not defined in the specification but there is support for the term "proteinase K" (see specification page 112, example 12). Amending the claims to include the term "proteinase K" would obviate the rejection. The term "SDSPG immunoaffinity chromatography blots" also has not been defined in the specification, for purposes of the instant

office action this term has been interpreted to mean SDS Page followed by electroblotting of the protein onto a membrane (see specification page 112, example 12).

Applicant should therefore specifically point out the support for any amendments made to the disclosure (see MPEP 2163.06).

Claims 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims utilize the terms "proteinase kinase" and "SDSPG immunoaffinity chromatography blots", however, the specification does not define these terms and the ordinary artisan would therefore not know metes and bounds of the claimed subject matter.

The term "proteinase kinase" is not defined in the specification but there is support for the term "proteinase K" (see specification page 112, example 12). Amending the claims to include the term "proteinase K" would obviate the rejection. The term "SDSPG immunoaffinity chromatography blots" also has not been defined in the specification, for purposes of the instant office action this term has been interpreted to mean SDS Page followed by electroblotting of the protein onto a membrane (see specification page 112, example 12).

Applicant should specifically point out the support for any amendments made to the disclosure (see MPEP 2163.06).

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please use 703-746-3162.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 11/12/03